NICE National Institute for Health and Care Excellence

NICE guidance

Osimertinib for adjuvant treatment of EGFR mutation-positive non-small-cell lung cancer after complete tumour resection

Technology appraisal guidance
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Your responsibility

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Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

This guidance replaces TA761.

1 Recommendation

1.1 Osimertinib is recommended, within its marketing authorisation, as an option for the adjuvant treatment of stage 1b to 3a non-small-cell lung cancer (NSCLC) after complete tumour resection. It is for adults whose tumours have epidermal growth factor receptor (EGFR) exon 19 deletions or EGFR exon 21 (L858R) substitution mutations. It is only recommended if:

- osimertinib is stopped at 3 years, or earlier if there is disease recurrence or unacceptable toxicity and
- the company provides it according to the commercial arrangement.

Why the committee made these recommendations

This evaluation reviews the evidence for osimertinib for treating NSCLC after complete tumour resection. It also reviews new evidence collected as part of the managed access agreement, which includes evidence from a clinical trial and from people having treatment in the NHS in England. During the managed access period and in the clinical trial, osimertinib was stopped after 3 years, or earlier if the cancer came back or there were severe side effects. So, this is how osimertinib will be used in the NHS.

People with EGFR mutation-positive NSCLC whose tumours have been surgically removed (complete resection) have the option of then having chemotherapy. There are no other options to have in addition to chemotherapy, so if a person does not have osimertinib they would have active monitoring.

A clinical trial comparing osimertinib with placebo shows that people who have osimertinib have less chance of their cancer coming back or getting worse, and live longer. But in the long term it is uncertain whether osimertinib is a cure or delays the cancer coming back.

The most likely cost-effectiveness estimates are within the range that NICE normally considers an acceptable use of NHS resources. So, osimertinib is recommended for routine use in the NHS.

2 Information about osimertinib

Marketing authorisation indication

2.1 Osimertinib (Tagrisso, AstraZeneca) is indicated for 'adjuvant treatment following complete tumour resection in adults with stage IB to IIIA NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics for osimertinib.

Price

2.3 The list price for osimertinib is £5,770 per 30 pack of 80-mg tablets (excluding VAT; BNF online accessed November 2024).

2.4 The company has a commercial arrangement. This makes osimertinib available to the NHS with a discount. The size of the discount is commercial in confidence.

3 Committee discussion

The evaluation committee considered evidence submitted by AstraZeneca, a review of this submission by the external assessment group (EAG), and responses from stakeholders. See the committee papers for full details of the evidence.

The condition

Epidermal growth factor receptor mutation-positive non-small-cell lung cancer

3.1 Non-small-cell lung cancer (NSCLC) accounts for around 80% to 85% of all lung cancers. People with an epidermal growth factor receptor (EGFR) mutation are at increased risk of recurrence, with particular risk of brain metastases. People with EGFR mutation-positive NSCLC tend to be younger than people with other types of NSCLC, so a treatment that delays or prevents recurrence or central nervous system (CNS) metastases is important. Around 8% to 16% of people with early-stage (1b to 3a) NSCLC have cancer that is EGFR mutation-positive. The patient experts outlined how earlier stage NSCLC can be asymptomatic for years with a wide range of symptoms developing later (such as cough, chest pain, difficulty breathing, weight loss, fatigue and bone pain). They explained that the fear of their cancer returning or spreading is a major source of anxiety and that the consequences of this happening can be devastating. They also highlighted that brain metastases can have particularly pronounced effects on their quality of life and can mean they must stop driving, limiting their ability to attend appointments. The committee agreed that people with EGFR mutation-positive NSCLC and their families would welcome new, effective treatments that lower the risk of recurrence.

Clinical management

Existing treatment pathway

3.2 Complete tumour resection is the preferred treatment for many people with early-stage EGFR mutation-positive NSCLC because it is potentially a cure. After complete tumour resection, people have the option of having adjuvant chemotherapy, which provides a small increase in overall survival (OS). The patient experts advised that the side effects of chemotherapy can be very difficult to manage and that people often dread this option. But they added that the thought of doing nothing after surgery and their cancer returning can cause significant anxiety and panic. They also advised that monitoring can help to lower anxiety, but because the frequency of scans varies between stages of disease, some people benefit less from this reassurance. There are no other options in the adjuvant setting. If people develop distant metastases after surgical resection, treatment options include chemotherapy or a tyrosine kinase inhibitor. The committee agreed that osimertinib as an adjuvant treatment may address an unmet need for people with EGFR mutation-positive NSCLC who have had a resection.

Active monitoring is an appropriate comparator

3.3 Osimertinib is a tyrosine kinase inhibitor that targets cancerous cells that have EGFR mutations, but has minimal activity against cells without these mutations. Clinical experts advised that osimertinib is an improvement in the management of EGFR mutation-positive disease. They expressed that osimertinib extends disease-free survival (DFS) and OS and is tolerable, with limited side effects that are also unlikely to lead to discontinuation of treatment. The patient experts agreed that osimertinib is a valuable, tolerable option and, combined with frequent monitoring, can lower some of the anxieties surrounding recurrence. They agreed that there are fears surrounding stopping osimertinib after 3 years and uncertainty about what this means for their risk of recurrence. The company outlined how osimertinib is not intended to displace adjuvant chemotherapy but instead be used in this setting with or without chemotherapy. There is therefore no alternative to osimertinib in this treatment space and the relevant comparator

is active monitoring. The committee concluded that active monitoring was the relevant comparator in this appraisal.

Clinical effectiveness

Osimertinib data sources

3.4 In the original evaluation, the main clinical-effectiveness evidence for osimertinib came from the ADAURA trial, a phase 3 randomised, double-blind, placebo-controlled, multicentre trial. ADAURA compared adjuvant osimertinib 80 mg (n=339) with placebo (n=343) for adjuvant treatment of stage 1b to 3a EGFR mutation-positive NSCLC after complete tumour resection in adults. Following a recommendation in the Cancer Drugs Fund (CDF), new evidence was collected as part of the managed access agreement. The current submission relies mainly on an updated data-cut of the ADAURA trial providing an additional 2 years of data for DFS and 3 years of data for OS. The Systemic Anti-Cancer Therapy (SACT) dataset collected data on people who had osimertinib in the NHS during the managed access period.

Clinical effectiveness in the osimertinib study

3.5 Evidence from ADAURA showed that, compared with placebo, osimertinib led to improvements in key clinical outcomes, including DFS and OS. The median DFS in the osimertinib arm was 65.8 months, while in the placebo arm it was 28.1 months (hazard ratio [HR] was 0.27; 95% confidence intervals [CI] 0.21 to 0.34). Median OS was not reached in the osimertinib arm or the placebo arm, but 5-year OS rates were 88% and 78%, respectively (HR was 0.49; 95% CI 0.34 to 0.70). Long-term effectiveness was a key uncertainty in the original appraisal and the EAG noted that there is still uncertainty in long-term DFS and OS. This is because of the low number of events in the osimertinib arm. Evidence from ADAURA showed that the gap between osimertinib and placebo DFS curves initially increases, but that the gap starts to decrease from around 36 months. It is possible that the gap will continue to decrease over time. Maturity rates (percentage of people experiencing the event) for osimertinib were 28% for DFS and 12% for OS. One

expert advised that although osimertinib will only slow recurrence for some people, this is still a meaningful benefit. The trial also reported data on CNS-specific DFS, in which osimertinib showed a significant improvement compared with placebo (HR was 0.36; 95% CI 0.23 to 0.57). The committee agreed that osimertinib improves key outcomes compared with placebo, but that there was considerable uncertainty around the extent to which the DFS benefit would continue beyond the period observed in the trial.

Subgroup clinical effectiveness in the osimertinib study

3.6 ADAURA reported evidence for stage 1b and stages 2 to 3a subgroups. The committee noted that for stages 2 to 3a, results were broadly similar to the overall population. But there was some uncertainty for the stage 1b subgroup, the benefit in DFS was smaller and rates of CNS-specific DFS were not reported. The EAG also expressed concern that subgroups were not included in the economic modelling. The committee agreed that it would have been useful to include subgroups in the economic modelling but that it was appropriate to use the overall population for decision making.

SACT dataset

3.7 The SACT dataset collected data on 143 people who had osimertinib between November 2021 and December 2022. The NHS England CDF clinical lead (from here, CDF lead) outlined that the population in SACT was older (median age 70 years) than the population in the ADAURA trial (median age 64 years). The number of people who had had prior chemotherapy was also much lower in the SACT dataset (27% compared with 60% in ADAURA). The EAG advised that this suggests some people may have been offered osimertinib instead of adjuvant chemotherapy. One clinical expert advised that some people would never have been offered chemotherapy, such as people who were too unwell to tolerate its side effects. Also, people with stage 1b NSCLC would not be offered cytotoxic chemotherapy and people with additional needs (such as needing renal function monitoring) could be more likely to be offered osimertinib. But, people would typically still be offered chemotherapy if they are young and fit enough to tolerate it. The experts also advised that the option of osimertinib may mean that

chemotherapy is stopped sooner if there are signs of cytotoxicity. The OS data maturity in SACT was only 6.2% by the April 2023 data cutoff. OS rates at 12 months were 92%, which is lower than those seen in ADAURA (95% at 36 months). The percentage of people on treatment was also lower in SACT than ADAURA at 12 months (75% compared with 96%) suggesting higher rates of people stopping treatment early. The committee discussed whether the data from SACT suggested osimertinib outcomes were more pessimistic in the real-world, but concluded that the data was too immature to make certain conclusions around this.

Economic model

Company's modelling approach

3.8 The company used a semi-Markov economic model for osimertinib and active monitoring. It comprised 5 states:

- disease-free
- locoregional recurrence (LRR)
- distant metastases first-line
- second-line distant metastases, and
- death.

The model structure included:

- a 37-year time horizon
- an assumption that people had active treatment on entry to the LRR or distant metastases health states
- an assumption that retreatment with first-line osimertinib in the distant metastases first-line health state is possible after 4 years (1 year after the maximum of 3 years on osimertinib), and

- a cure assumption (see section 3.13).

The committee concluded that the model structure was appropriate for decision making but that there were concerns with the modelling of the cure assumption.

Extrapolating DFS and OS

3.9 The company used different distributions and different sources of data to inform the probability of transitions between the health states in the model. ADAURA DFS data was used to inform the choice of distribution for moving from the disease-free state to the LRR or distant metastases first-line health states. The FLAURA trial, which assessed the use of osimertinib in the metastatic setting, was used to inform the risk of mortality in the distant metastases health states (first- and second-line). The risk of mortality was constrained by general population rates in the UK. Risk of mortality in the disease-free and LRR health states was assumed to be the same as the UK age- and sex-matched general population. The EAG had concerns that the predicted data was not a good match for the data observed in the ADAURA trial. It suggested that alternative choices of distributions would improve this to an extent, but a key limitation was the choice of model form. The EAG explained that the model form selected by the company was very rigid and could not account for the complexities seen in the ADAURA data. For example, ADAURA hazards for the risk of developing LRR suggested 2 turning points for people having osimertinib, but the model only allowed for 1. Also, for people having active monitoring, none of the distributions provided a good fit to the data for transitioning between the disease-free and distant metastases first-line health states. For osimertinib, the EAG argued that alternative distribution choices offer better matches to the observed data. But the company argued that these alternatives are overly influenced by longer-term trial data, which is uncertain because of the small number of people still at risk of recurrence and being followed up. The committee was concerned that these limitations lead to uncertainty in the modelling of long-term outcomes and could introduce inaccuracy. It concluded that this uncertainty was largely unresolvable without longer-term data.

Retreatment with osimertinib

3.10 The company's original model assumed that retreatment with osimertinib was possible but only from 4-years after starting treatment. It also assumed that 50% of people who have a distant recurrence after this point would have osimertinib. The company also assumed that 83% of people who have a distant recurrence after being assigned to the active monitoring arm would have osimertinib. The EAG base case has the same assumptions. But it advised that it is likely a much higher percentage of people would have retreatment and that their clinical advisers suggested the vast majority would. The EAG did scenario analyses varying the rates of retreatment. Increasing the percentage of people having retreatment consequentially increases the incremental cost-effectiveness ratio (ICER). Data on retreatment was not collected in the SACT dataset. But, the CDF lead advised that despite osimertinib only being available in the CDF for 3 years, around 7% (33 people) of those who had osimertinib had already had retreatment. They advised that this suggests that retreatment is happening before 4 years, and noted that retreatment was only allowed if a person did not previously progress on osimertinib. One clinical expert agreed that it is likely that the vast majority of people would have retreatment. They added that retreatment is particularly likely if the person stops treatment early or has low-level toxicity. But people with adverse reactions to treatment or those with brain metastases may be less likely to have retreatment. The company outlined that in ADAURA, 41% of people in the osimertinib arm who had any subsequent treatment had osimertinib. But, the EAG advised that it was unclear how many of these people had previously progressed on osimertinib. The committee also noted that it was unclear whether osimertinib was available in the metastatic setting in all of the countries where the ADAURA trial was done. It added that the trial did not initially allow people in the active monitoring group to have subsequent osimertinib. The committee agreed that it is likely that much more than 50% of people would have osimertinib as a retreatment in the metastatic setting. The committee agreed that 70% would be a more reasonable estimate. It also agreed that it was implausible that retreatment would only be started after 4 years (after first starting osimertinib), noting evidence from the CDF lead. The committee concluded at the first meeting that the model should allow retreatment from 3 years. At consultation, the company revised its base case. The revised base case assumed that 60% of people who have a distant recurrence would have retreatment with osimertinib and retreatment could start after 3.5 years. It argued that retreatment

immediately after completing 3 years of adjuvant osimertinib treatment is clinically implausible because a delay would be needed during diagnosis of recurrence. The EAG advised that a retreatment timepoint of 3.5 years may be reasonable and the true proportion who will have retreatment remains unknown. At the second committee meeting, a clinical expert said that a retreatment rate between 50% and 60% was reasonable. The committee concluded that it was plausible that:

- 60% of people having treatment in the metastatic setting who previously had osimertinib would be offered retreatment, and
- retreatment with osimertinib could start from 3.5 years.

But, both of these values were uncertain.

3-year stopping rule

3.11 The original appraisal included a 3-year treatment stopping rule in its model and this was again included in the company model. This is based on the trial design of ADAURA, where the maximum possible treatment duration was 3 years. It is also stated in the summary of product characteristics for osimertinib that treatment for more than 3 years was not studied. The clinical experts said that adjuvant treatment could not be indefinite and that the 3-year time period is appropriate. They also noted that some people would stop sooner in cases of high toxicity but noted that in their experience these people often respond well to osimertinib. They added that these risks and rewards must be balanced against each other. The committee noted that in ADAURA, 13% of people on osimertinib stopped because of toxicity compared with 3% in the placebo group. The patient expert explained that some people would find stopping treatment difficult because they would fear the disease coming back. The committee concluded that a 3-year treatment stopping rule was acceptable.

Starting age

3.12 The committee recalled that people in the SACT dataset were, on average, 6 years older than the people in ADAURA (see section 3.7). The company

modelling used 63 years as the starting age on entry to the model, based on ADAURA. The committee was concerned that this might underestimate the average age of people having treatment. This has implications for cost-effectiveness estimates because a starting age of 70 years would mean that the average remaining life expectancy would be lower. The impact of starting age is particularly important. This is because the cure assumptions in the model mean that the younger the starting age, the longer the survival and quality of life benefits last for people who are cured. It agreed that a starting age of 70 years would be more reflective of what would be expected in the NHS because this is what was seen in SACT. The committee was aware that for baseline clinical data the SACT data is ranked higher than the ADAURA data according to NICE's Decision Support Unit Technical Support Document 13. The committee concluded that the economic model should use a starting age of 70 years, which would also lower the time horizon of the model by 7 years (to 30 years). At consultation, the company maintained a starting age of 63 years. It argued that the data from SACT was too immature, based on a small sample size and inconsistent with other key parameters in the model. It provided evidence from a 2024 survey of 233 EGFR Positive UK members, which reported a median age at diagnosis of between 60 and 64 years. At the second meeting, EGFR Positive UK reported updated survey data from over 300 people that showed an average age closer to 63 years. The EAG did not consider the evidence applicable, because the majority of those surveyed would not be eligible to have adjuvant osimertinib because they had stage 4 disease at diagnosis. The EAG agreed that a starting age of 70 years introduces some inconsistency in evidence sources in the model. This is because the trial data used to model the effectiveness of treatment is based on a younger population. But it noted that the SACT data should reflect the age of people having osimertinib in the NHS. At the second committee meeting, the CDF lead explained that the latest SACT data showed a median age of 71 years and mean age of 69.2 years. This was for the 518 people who had osimertinib for resected EGFR-mutation-positive NSCLC from May 2021 to September 2024. The committee considered the evidence provided by the CDF lead to be the most reliable estimate of starting age, with a large enough sample size to draw conclusions from. It acknowledged that this leads to an inconsistency of sources in the model. This is because the trial data used to model the effectiveness of treatment is based on a younger population. But, DFS may be longer in younger people, and this is not adjusted when the starting age in the model is adjusted. So the impact of this inconsistency could be that there

is potentially additional benefit modelled for osimertinib than is seen in the NHS. Overall, the committee agreed that adjusting the starting age in the model to reflect the real-world NHS data was reasonable. This approach ensures that the modelled benefits are more likely to reflect those seen when osimertinib is used in the NHS. So the committee concluded that a starting age of 69.2 years based on NHS data should be used.

Cure assumptions

Company and EAG approaches

3.13 The company applied a cure timepoint in the model. The company base case used the following cure timepoints:

- 5 years in the active monitoring arm
- 8 years in the osimertinib arm.

The company advised that the difference in these final cure points was to account for the extra 3 years during which the person would have osimertinib. Projected rates of recurrence up to the end of year 4 for both active monitoring and osimertinib groups were based on DFS curves from the ADAURA trial. After the cure timepoint, the modelled risk of recurrence was adjusted to 5% of the projected risk from the ADAURA data. This was intended to represent 95% of the population assumed to be cured and free of risk of recurrence from the cure timepoint. The company included a 'warm-up' period beginning after 4 years. During the warm-up period the chance of recurrence decreases roughly linearly to 5% of the projected risk from the ADAURA trial. This happens by the final cure-point of 5 years for active monitoring and 8 years for osimertinib (see section 3.14). The EAG commented that the company approach to modelling cure was unconventional. It noted that, usually, a mixture-cure model is used in which a 'cured' group is exposed to different risks of recurrence to a 'non-cured' group. In the absence of an alternative model structure, the EAG presented 2 scenarios:

- an optimistic scenario, which was the same as the company's base case, and
- a pessimistic scenario, which had a cure timepoint of 8 years for osimertinib and no warm-up period.

It explained that it is likely that an appropriate model cure-point probably falls somewhere between the optimistic and pessimistic scenarios. The EAG also presented scenario analyses in which the osimertinib cure-point was lowered to 7 years and to be equivalent to how long someone is on treatment plus 5 years. Neither of these scenarios had an explicit warm-up period. The committee was concerned with the model structure used by the company, and agreed with the EAG that it was unconventional to model cure this way. But it agreed that decision making should be based on this model structure, in the absence of an alternative. It concluded that decisions had to be made on:

- whether there is evidence of cure in the data for either osimertinib or active monitoring (or both)
- the timepoint from which this cure should be applied (if at all), and
- whether a warm-up period should be applied.

Warm-up period

3.14 The company included a warm-up period because without it, people in the model reach the final cure-point (see section 3.13) and suddenly have a huge drop in risk of recurrence. The company argued that this is not plausible. It suggested that although the 4-year timepoint (when a person's risk begins to fall after staying in the disease-free state) is arbitrary, it is more logical than a sudden drop. At the first committee meeting, one clinical expert advised that a warm-up period should be included. They explained that this is because follow up in clinical practice is often only 5 years. By this timepoint, the risk of recurrence is low, the number of subsequent events is small, and a durable response is expected. But they added that the timepoint from which a warm-up period would begin is unclear. The EAG explained, using the smoothed hazard plots, that the ADAURA trial shows that for active monitoring the risk of recurrence starts high and falls

over time. But, for osimertinib it starts lower and increases. The committee agreed that this suggests that, compared with active monitoring, for some people osimertinib only slows recurrences. It is also possible that there is a rebound effect that causes recurrence risk to increase after stopping treatment. The EAG advised that although it is not impossible that a plateau would emerge for osimertinib, the data does not show a clear cure-point in the hazards for recurrence. So a warm-up period from 4 years is unlikely. The company also noted that a warm-up period had been considered in the NICE technology appraisal for trastuzumab emtansine for adjuvant treatment of HER2-positive early breast cancer and NICE technology appraisal for nivolumab with chemotherapy for neoadjuvant treatment of resectable non-small-cell lung cancer. The EAG advised that in those appraisals, the warm-up period assumption had a relatively small impact on the ICER. It also noted that in those appraisals the cure points and warm-up periods for the treatment and comparators were the same. But for this appraisal it has a much bigger impact and the cure timepoints and warm-up period are different between treatments. The committee noted that applying a warm-up period has implications for long-term modelling of outcomes. This creates a substantial gap in DFS between osimertinib and placebo that extends decades into the future. It noted that there was a lack of support for this in the observed data and that the warm-up period started after 4 years for both treatment groups. This is despite the risk of recurrence increasing between 4 years and the end of follow up in the osimertinib arm of the ADAURA data. Also, many people in that group will only just have finished treatment. The committee agreed that the company's approach to modelling cure had considerable limitations. It concluded there was uncertainty about DFS modelling and that a warm-up period should not be applied.

Final cure timepoint

3.15 The company submission included a cure at 5 years for active monitoring and 8 years for osimertinib. The company stated that the ADAURA DFS data shows a plateau forming after 48 months for people having placebo, suggesting a very small remaining risk of recurrence after this point. The company advised that a plateau is also expected for osimertinib at a later timepoint. But interpretation of the trial data beyond 48 months is limited by the small number of people who are still being followed up. The EAG highlighted that there is insufficient evidence to

determine a cure assumption for osimertinib. It noted that the risk of recurrence for people who had osimertinib was still increasing at 5 years in the ADAURA trial. The EAG used individual patient data from ADAURA to create mixture-cure models to test the plausibility of cure in each group. It found that for active monitoring, a cure could be modelled using most distributions. But for osimertinib, most distributions failed to model a cure, suggesting insufficient DFS data to support this assumption. Clinical experts advised that the 5-year timepoint is a pragmatic choice. This is because it coincides with the timepoint in clinical practice from which routine follow up can be stopped because the risk of subsequent events is low enough. One expert agreed that an 8-year timepoint for osimertinib is also reasonable because it contains the 5-year follow up plus the 3-year treatment duration. The clinical experts agreed that for some people it would only slow recurrence, but it is also plausible that it would lower the recurrence rate overall compared with active monitoring. It is also plausible that some people will not have recurrence and that most recurrences would be expected in the first few years after stopping osimertinib. The committee agreed that there was uncertainty surrounding when, if at all, people who had osimertinib could be considered cured. This is because it is unclear whether, in the long term, recurrence rates for people having osimertinib would gradually decrease to the same rate as those having active monitoring. The committee recalled their preference to not apply a warm-up period (see section 3.14). It considered a scenario in which no warm-up period was applied with a cure timepoint for osimertinib at 8 years. This generated DFS outcomes that implied no increase in the proportion of people remaining disease-free in the long term after having osimertinib. The committee agreed this was a conservative assumption. So it considered an EAG scenario in which the timepoint was lowered to less than 8 years (5 years plus the model estimate of time on treatment). This was to reflect that not all people completed a full 3 years on treatment. The committee felt that this scenario generated DFS outcomes that were more plausible and noted that it lowered the ICER. The committee concluded at the first meeting that this should be included in the model because using the 8-year timepoint without warm-up would be too conservative. The committee noted the uncertainty surrounding this assumption and that an alternative model structure would have been preferred. At consultation, the company provided additional scenario analysis where the cure timepoint for active monitoring was 5 years, and 5, 6, 7, and 8 years for osimertinib with no warm-up period. At the second committee meeting, a clinical expert suggested that the cure timepoint should be 5 years for

both arms. This is because this is when people would usually be discharged from active monitoring. But they explained this does not necessarily indicate a cure and a small number of people can have a late relapse. The committee recalled the explanation from the EAG (see section 3.14), using the smoothed hazard plots from ADAURA, that for osimertinib the risk of recurrence increases over time. The committee noted that cure modelling beyond the trial data was highly uncertain and discussed several cure timepoints between 5 and 8 years with no warm-up period. It concluded that because the risk of recurrence in the ADAURA trial continued to rise at 5 years, a cure timepoint of 5 years for osimertinib was not plausible. It also maintained that a cure timepoint of 8 years was too conservative. The committee considered that it is plausible that the risk of recurrence will start to drop beyond 5 years. But there is no strong basis for any cure timepoint without further follow-up data. The committee concluded that a cure timepoint of 5 years for active monitoring and between 6 and 7 years for osimertinib is plausible but acknowledged this is highly uncertain.

Other factors

EGFR testing

3.16 The company did not include the costs associated with testing for EGFR mutations in their economic model. It argued that these mutations are already routinely tested for in the NHS by next generation sequencing panel tests, so the tests do not represent additional costs for osimertinib. One clinical expert advised that people with EFGR-positive cancer would not be offered neoadjuvant treatment. So EGFR status would typically be tested for in addition to other mutations before any treatment is offered. The CDF lead advised that because people with stage 1b disease are not eligible for neoadjuvant treatment, these people may not be tested routinely. They advised that some of the testing costs for EGFR should be included in the model, though the appropriate proportion to apply costing to is unclear. The committee concluded that additional costs associated with EGFR testing should be included in the model. At consultation, the company maintained that EGFR testing costs should not be included in the model. The company stated that healthcare professionals interviewed in 2023 confirmed that testing is part of routine practice and is done before surgery

where possible. The EAG agreed that most people would have routine testing but that some testing costs are attributable to adjuvant osimertinib, likely in people with stage 1b disease. At the second committee meeting, the CDF lead advised that before osimertinib entered the CDF, people with stage 1b NSCLC did not routinely have EGFR testing, but not all testing costs are attributable to osimertinib. One clinical expert suggested that EGFR testing is routine before someone has adjuvant treatment. Another explained that there are some people who need additional testing, but most is done routinely. The committee considered the input from clinical experts and the CDF lead and noted that the inclusion of EGFR testing costs had a small impact on the ICER. The committee concluded that EGFR testing costs should be included for people with stage 1b disease in the model.

Equality

3.17 It was noted that EGFR mutations are more common in younger people, Asian populations and women. The committee noted that the issue of different disease prevalence cannot be addressed in a technology appraisal.

Uncaptured benefits

3.18 The committee recognised that osimertinib represents an effective treatment option for people with EGFR mutation-positive NSCLC who have had complete resection and would otherwise have limited options. The evidence showed that it is associated with improvements in key clinical outcomes. But, the committee concluded that all benefits of treatment with osimertinib were captured in the model.

Severity

3.19 The committee considered the severity of the condition (the future health lost by people living with the condition and having standard care in the NHS). The committee may apply a severity modifier (a greater weight to quality-adjusted life years [QALYs]) if technologies are indicated for conditions with a high degree of

severity. Neither the EAG nor the company made a case for a higher-than-normal severity modifier to be applied to this disease area. So, the committee concluded that a severity weight of 1.0 applied to the QALYs was appropriate.

Cost-effectiveness estimates

Acceptable ICER

3.20 NICE's manual on health technology evaluations notes that, above a most plausible ICER of £20,000 per QALY gained, decisions about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. The committee noted several uncertainties, that data collection in the CDF had not resolved, specifically regarding:

- long-term DFS and OS (and uncertainty around cure; see section 3.15)
- rates of retreatment and time from which retreatment occurs.

Because of the uncertainty in the cost-effectiveness estimates, the committee agreed that an acceptable ICER would be around £20,000 per QALY gained when compared with active monitoring.

Committee's preferred assumptions

3.21 The committee's preferred model assumptions were:

- using the EAG's corrections for model and costing errors (including having EGFR testing costs for stage 1b disease)
- no warm-up period prior to cure
- cure-point of 5 years for active monitoring
- cure-point of between 6 and 7 years for osimertinib

- retreatment allowed from 3.5 years after starting osimertinib, in line with the company's revised base case
- 60% of people in the osimertinib group who develop distant metastases will have osimertinib in the first-line setting, in line with the company's revised base case
- starting age of 69.2 years in the economic model.

The company's base-case ICERs for osimertinib compared with active monitoring were below £20,000 per QALY gained (because of confidential discounts, the exact ICERs are confidential and cannot be reported here). The ICERs were around £20,000 per QALY gained when the committee's preferred assumptions were used. Increasing the starting age had the biggest impact on the ICER. All other changes had a small effect, including moving from the company's cure assumptions to the committee's preferred assumptions of no warm-up period and a cure-point between 6 and 7 years.

Conclusion

Recommendation

3.22 The clinical-effectiveness evidence showed that osimertinib improved key outcomes in people with EGFR mutation-positive NSCLC. The committee concluded that the ICER that included its preferred assumptions was within the range that NICE considers an acceptable use of NHS resources (see section 3.19). So, osimertinib is recommended.

4 Implementation

4.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 3 months of its date of publication.

4.2 Chapter 2 of Appraisal and funding of cancer drugs from July 2016 (including the new Cancer Drugs Fund) – A new deal for patients, taxpayers and industry states that for those drugs with a draft recommendation for routine commissioning, interim funding will be available (from the overall Cancer Drugs Fund budget) from the point of marketing authorisation, or from release of positive draft guidance, whichever is later. Interim funding will end 90 days after positive final guidance is published (or 30 days in the case of drugs with an Early Access to Medicines Scheme designation or cost comparison evaluation), at which point funding will switch to routine commissioning budgets. The NHS England Cancer Drugs Fund list provides up-to-date information on all cancer treatments recommended by NICE since 2016. This includes whether they have received a marketing authorisation and been launched in the UK.

4.3 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final draft guidance. When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has completely resected stage 1b to 3a non-small-cell lung cancer that has an epidermal growth factor receptor exon 19 deletion or exon 21 (L858R) substitution mutation, and the healthcare professional responsible for their care thinks that osimertinib is the right treatment, it should be available for use, in line with NICE's recommendations.

5 Evaluation committee members and NICE project team

Evaluation committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee D.

Committee members are asked to declare any interests in the technology being evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

The minutes of each evaluation committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Chair

Megan John
Chair, technology appraisal committee D

NICE project team

Each evaluation is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the evaluation), a technical adviser and a project manager.

Tom Jarratt and Sally Lewis
Technical leads

Christian Griffiths and Michelle Green
Technical advisers

Kate Moore and Louise Jafferally
Project managers

Ross Dent
Associate director

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